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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

TRUONG, TAMTHOM NGO

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/918,039	Applicant(s) CHOI-SLEDESKI ET AL.	
	Examiner Tamthom N. Truong	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 65-41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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Applicant's amendment of 7-5-06 has been fully considered. Although the amended claims have overcome the previous rejections of 112/1st and 2nd paragraph, new issues of 112 are noted.

Claims 1-34 are cancelled.

Claims 35-41 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 35-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 35 recites the limitation of "condition of the arterial or venous vasculature" because defining a disease by its underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood. The test for determining compliance with 35 USC 112 2nd paragraph is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

b. Also, positions of X_5 , X_{5a} , X_{5b} are inconsistent with the requirement in claim 35.

In said requirement, one of the X's must be on the pyrrolo ring. However, by the structure all three X's are on the pyridine ring.

c. In claim 35, the scope of Y^1 and Y^2 forming a heterocycle has indefinite metes and bounds because it is not clear whether the N (they are attached to) is the only heteroatom, or if there are additional heteroatoms.

d. Still in claim 35, the term "heteroalkyl" has indefinite metes and bounds because the specification does not define such a term. It is unclear if such a group bonded to A_4 via a heteroatom or a carbon atom.

e. Claim 37 recites the term "prodrugs" which has indefinite metes and bounds. It is not clear what constitutes a prodrug. Furthermore, claim 37 lacks antecedent basis because "prodrugs" are not recited in claim 35 or 36.

f. Claim 41 also recites the term "prodrugs" which has indefinite metes and bounds. It is not clear what constitutes a prodrug. Furthermore, claim 41 lacks antecedent basis because "prodrugs" are not recited in claim 39 or 40.

g. Claim 38 recites "hirudin derivatives and analogs thereof" which have indefinite metes and bounds because the specification does not define what those compounds are.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of *thrombotic occlusion*, and *thromboemolism*, does not reasonably provide enablement for other diseases related to venous and arterial vasculature such as: arthritis, cancer, Alzheimer's disease, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

- (1) The breadth of the claims;
- (2) The amount of direction or guidance presented;
- (3) The state of the prior art;
- (4) The relative skill of those in the art;
- (5) The predictability or unpredictability of the art;
- (6) The quantity of experimentation necessary;

[See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

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Claim 35 recites: "A method for treating...a condition of the arterial or venous vasculature capable of being modulated by inhibiting an activity of Factor Xa... comprising administering to the patient a therapeutically effective amount of a pyrrolopyridine compound having the structure...wherein said compound is administered in combination with at least one other agent selected from diagnostic agents, cardioprotective agents, direct thrombin inhibiting agents, anticoagulant agents, antiplatelet agents, and fibrinolytic agents."

The action intended by the inhibition of Factor Xa includes more than anticoagulant therapy. According to the specification, such an action includes "*chronic and degenerative diseases as arthritis, cancer, atherosclerosis, restenosis post coronary angioplasty and Alzheimer's disease...*" Thus, not only claim 35 recites broad scope of compounds, but also a broad scope of diseases as well as additional agents. Therefore, the scope of claim 35 is unduly broad.

Claims 36-38 depend on claim 35, and recite specific additional agents. However, their scopes are still unduly broad in terms of the claimed compounds, and diseases related to Factor Xa.

Like claim 35, claim 39 recites a pharmaceutical composition comprising the claimed compounds and "*at least one other agent selected from diagnostic agents, cardioprotective agents, direct thrombin inhibiting agents, anticoagulant agents, antiplatelet agents and fibrinolytic agents.*" The scope of the compounds recited in claim 39 is just as broad as that recited in claim 35. With the combination of so many agents, the scope of claim 39 is unduly broad.

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Claims 40 and 41 depend on claim 39, and recite specific additional agents, but still have the broad scope of the compounds. Therefore, the scopes of claims 40 and 41 are unduly broad as well.

The amount of direction or guidance presented:

Although the specification provides the guidance for making the claimed *pyrrolo[2,3-c]pyridine* compounds, as exemplified by the elected species in Example 48. However, regarding the activity of such a compound as inhibitor of Factor Xa, the specification does not provide any IC₅₀ value of such a compound. The specification only describes bioassay procedures without disclosing any tested *pyrrolo[2,3-c]pyridine* compounds. The only compound actually tested was a compound of substituted *1,6-diaminoisoquinoline*. Although *isoquinoline* is a bicycle, its structure is not equivalent to that of *pyrrolo[2,3-c]pyridine*. Thus, the activity of isoquinoline cannot be extrapolated to that of *pyrrolo[2,3-c]pyridine*. As for the combination of the claimed compounds and other agents, the specification does not teach how the claimed compounds can be combined and at what dosage. Thus, the specification fails to provide sufficient guidance for one skilled in the art to make such a pharmaceutical composition as recited in claims 39-41, and use it in a broad method as recited in claims 35-38.

The state of the prior art:

Although anticoagulant agents can often be combined in the clinical setting, such a combination is often done for a short term (e.g., post-op telemetry), and with close monitoring of the prothrombin time. Some anticoagulant agents can interfere by displacing or competing with each other for protein binding, and thus, could alter the bioavailability of each other. For

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example, warfarin is known to alter other drug's bioavailability by competing for protein binding. While blood clot does not have a desirable effect, too little clotting could lead to hemophilia, which could be just as detrimental.

Furthermore, as evident by the teachings of **Baker et. al.** (US 5,854,268), and **Chambers et. al.** (US 5,604,240), the compounds of *pyrrolo[2,3-*c*]pyridine* have the activity of selective agonists of 5-HT₁ receptors, and not inhibitors of Factor Xa. Thus, the current practice of medicine and state of the prior arts do not seem to support the pharmaceutical composition and method of treatment recited in claims 35-41.

The relative skill of those in the art:

Even with the advanced training, the skilled clinician would have to carry out extensive research to select an effective compound from the large Markush group of formula I. Not only one has to determine an IC₅₀ value, but also *in-vivo* activity to establish an LD₅₀, therapeutic index and pharmacokinetic profile for each compound. Once an effective compound is identified, the skilled clinician would have to evaluate the combination of said compound with any of the additional agents listed in claims 35-41. Given a large Markush group of the claimed formula I, and the multiple combinations, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the

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instant case, the specification only describes bioassays without indicating any tested compounds of *pyrrolo[2,3-c]pyridine*. However, said description alone does not adequately guide the skilled clinician in the treatment of diseases that are allegedly related to Factor Xa which includes cancer, and Alzheimer's disease. Thus, with such a limited teaching, the skilled clinician would have to carry out undue experimentation to make a pharmaceutical composition by combining agents as recited in claims 39-41, and use it in the methods recited in claims 35-38.

3. **Scope of Enablement:** Claims 35-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the making and using of compounds of the claimed formula wherein the *pyrrolidin-2-one* ring is substituted with an amino or amide, does not reasonably provide enablement for the making and using of compounds of formula II wherein the *pyrrolidin-2-one* ring is substituted with other moieties, ring and functional groups. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

- (1) The breadth of the claims;
- (2) The amount of direction or guidance presented;
- (3) The state of the prior art;
- (4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 35 recites: "A method for treating ... comprising administering a therapeutically effective amount of a ...pyrrolopyridine compound having the formula..." Note, the pyrrolo portion is substituted with several substituents represented by variables X_1 , X_{1a} , X_3 , X_4 , R_1 and R_2 . Note also, R_1 represents many moieties, rings and groups having Y^1Y^2N which can form a ring. Thus, on the pyrrolo portion, the compound can be extensively substituted with complex moieties, and the final structure could go beyond pyrrolidinone-(pyrrolopyridine). Therefore, the scope of claim 35 is unduly broad.

Claims 36-38 depend on claim 35 for the scope of compounds with the same broad scope.

Claim 39 recites "A pharmaceutically composition..." of the same formula with such an unduly broad scope.

Claims 40 and 41 depend on claim 39 and have the same unduly broad scope for compounds.

The amount of direction or guidance presented:

Regarding the preparation of compounds of the claimed formula, the specification provides the starting material for the pyrrolidine ring as being already substituted (see formula II). The specification is silent as to the availability of necessary reactants needed to prepare a

compound of formula II with substituents on it. Note, **In re Howarth** 210 USPQ 689; **Ex parte Moersch** 104 USPQ 122, for the need to show starting material sources commensurate with the claims' scope.

Regarding the biological activity, the specification only details various bioassay methods without indicating which compounds have been tested. Assuming all compounds in the working examples have been tested, their activity cannot be extrapolated to other compounds of the claimed formula II wherein the pyrrolidinone ring is extensively substituted as there is no evidence of recognized biological equivalency for such diverse groups.

Thus, the specification does not provide sufficient enablement commensurate with the broad Markush group of the claimed formula.

The state of the prior art:

Typically, *pyrrolo[2,3-c]pyridine* compounds are known as selective agonists of 5-HT₁ receptors as evident by **Baker et. al.** (US'268) and **Chambers et. al.** (US'240) cited in the rejection above. Thus, the state of the prior art does not provide adequate enablement for making compounds in commensurate with the scope of the claimed formula and use them to treat a condition of the arterial or venous vasculature.

The relative skill of those in the art:

Even with the advanced training, the skilled medicinal chemist and/or clinician would have to carry out extensive research to make an array of compounds of the claimed formula, and select an effective compound from such a large Markush group for treating arterial or venous vasculature. Not only one has to determine the inhibitory activity on factor Xa, but also *in-vivo*

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activity to establish an LD₅₀, therapeutic index and pharmacokinetic profile for each compound. Given a large Markush group of the claimed formula, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the specification does not provide starting materials for making compounds of the claimed formula with complicated substituents on the pyrrolidinone ring. It also fails to provide biological data for using the claimed compounds in a method of treating a condition of arterial or venous vasculature. Thus, with the large Markush group of the claimed formula, without the guidance for starting material sources of pyrrolidinone and substituents thereon, undue experimentation is necessary for making such an array of compounds as well as establishing biological activity for those compounds as inhibitors of factor Xa.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

*Tamthom N. Truong**Examiner**Art Unit 1624*

12-7-06

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